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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,692	01/25/2001	Anne Charlotte Arentsen	6124.200-US	5360

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EXAMINER
MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,692	ARENTSEN, ANNE CHARLOTTE	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, PRELIMINARY AMENDMENT, SEQUENC ELISTING, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. This application claims priority under 35 U.S.C. § 119 for U.S. Provisional application No. 60/183,300 having a filing date of 2/17/00 and Danish application No. PA 2000 00156 having filing date of 1/31/00. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The preliminary amendment and sequence listing filed 7/29/03, and the information disclosure statement (IDS) and Form PTO-1449 filed 5/7/01 and 7/20/01, respectively are acknowledged, entered and considered. In view of Applicant's request claims 3-11 have been amended. Thus, claims 1-15 is present for examination.

DISCLOSURE OBJECTED TO, MINOR INFORMALITIES

2. The disclosure is objected to because of the following informalities: on page 14, line 12, I the recitation "optainable". It is believed to be typographical error. Appropriate correction is required.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5-8 and 11-15 are indefinite in the recitation the acronyms "GLP-1" (claims 1-3, 5-8 and 12-15), "HPLC" (claim 5) and "DMSO" (claim 11). Use of full terminology at least in first occurrence would obviate this rejection.

Claim 2 is indefinite and confusing in the recitation ".....adjusting pH to pI-4<pH<pI, or to pI<pH<pI+4, wherein pI is the isoelectric point of the GLP-1analogue" because it is not clear how the pH is adjusted to pI-4 or <pH<pI+4. Appropriate clarification is required.

Claim 13 is indefinite in the recitation "optainable". It is believed to be typographical error. Appropriate correction is required.

CLAIMS REJECTION-35 U.S.C. § 102(b)

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, 7, 9-11, 13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/30731.

The reference of WO 99/30731 discloses process for producing crystals of GLP-1 analog which involves preparing an aqueous solution comprising a GLP-1 analog, a salt, and an organic solvent including a homogenous composition of GLP-1 crystals for pharmaceutical formulation thereof (See e.g., page 3, lines 22 to page 4, lines 20). Thus, meeting the limitations of claims 1, 11, 13 and 15. Also, the reference discloses

on page 9, lines 28-33 similar crystal length as claimed in claim 4 since the claim is directed to crystals having a length of at least 0.5 μm. On page 10, the reference states that biosynthetic GLP-1 analogs are preferred, thus, meeting the limitation of claim 7, which is directed to non-synthetic GLP-1 analogs. Further, on pages 11 to pages 14, the prior art clearly discloses the use of various organic solvents, buffers, and salts, wherein the organic solvent is present in a concentration of from 0.5 to 50 % v/v, wherein the GLP-1 analog in the aqueous solution is present in a concentration of at least 0.5 mg/ml, and wherein the salt is present in a concentration of at least 25 mM as directed to claims 6, and 9-11. On page 15, lines 9 to 11, the pH is adjusted from a mildly acidic pH to a mildly basic pH, and as such meets the limitation of claim 2. Thus, in the absence of evidence to the contrary, the claimed process for producing crystals of GLP-1 and crystals formulation thereof disclosed by the reference anticipates claims 1-2, 4, 6-7, 9-11, 13 and 15 as drafted.

5. Claims 1, 3-4, 6 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 619 322

EP 0 619 322 discloses a process for the production crystals of a GLP-1 analog by mixing solutions of GLP-1 in buffer with certain combination salts and organic solvents resulting in a needle shaped crystals of GLP-1 analog, wherein the crystals has a length of at least 0.5 μm and wherein the GLP-1 analog in the aqueous solution is present in a concentration of at least 0.5 mg/ml (See e.g., pages 20-21 and 36-40) as directed to claims 1, 3-4 and 6. On Example 45, the reference clearly discloses the product of needle shaped crystals of a GLP-1 analog as claimed in claim 14. Thus, in the absence of evidence to the contrary, the claimed process for producing crystals of

GLP-1 and crystals formulation thereof disclosed by the reference anticipates claims 1-, 3-4, 6 and 14 as drafted.

6. Claims 1, 5, 11, 13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Pridal et al., (International Journal of Pharmaceutics, Vol. 136, pp. 53-59, 1996).

The reference of Pridal et al., discloses process for producing crystals of GLP-1 analog which involves preparing an aqueous solution comprising a GLP-1 analog, a salt, and an organic solvent including a homogenous composition of GLP-1 crystals for pharmaceutical formulation thereof (See e.g., pages 54 –55). Thus, meeting the limitations of claims 1, 11, 13 and 15. On page 54, left column, last paragraph, the reference clearly states that the purity of GLP-1 was determined by capillary electrophoresis and analytical HPLC was <95%, and as such meets the limitation of claim 5 which is directed to a GLP-1 analog in the aqueous solution having a purity of less than 95% as measured by HPLC. Thus, in the absence of evidence to the contrary, the claimed process for producing crystals of GLP-1 and crystals formulation thereof disclosed by the reference anticipates claims 1, 5, 11, 13 and 15 as drafted.

CLAIMS REJECTION-35 U.S.C. § 103(a)

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/30731 taken with EP 0 619 322 or Pridal et al., (International Journal of Pharmaceutics, Vol. 136, pp. 53-59) or WO 98/08871.

WO 99/30731 teaches similarly as the instantly claimed invention process for producing crystals of GLP-1 analog which involves preparing an aqueous solution comprising a GLP-1 analog, a salt, and an organic solvent including a homogenous composition of GLP-1 crystals for pharmaceutical formulation thereof (See e.g., page 3, lines 22 to page 4, lines 20). Thus, meeting the limitations of claims 1, 11, 13 and 15. Also, the reference discloses on page 9, lines 28-33 similar crystal length as claimed in claim 4 since the claim is directed to crystals having a length of at least 0.5 μm. On page 10, the reference states that biosynthetic GLP-1 analogs are preferred, thus, meeting the limitation of claim 7, which is directed to non-synthetic GLP-1 analogs. Further, on pages 11 to pages 14, the prior art clearly discloses the use of various organic solvents, buffers, and salts, wherein the organic solvent is present in a concentration of from 0.5 to 50 % v/v, wherein the GLP-1 analog in the aqueous solution is present in a concentration of at least 0.5 mg/ml, and wherein the salt is present in a concentration of at least 25 mM as directed to claims 6, and 9-11. On page 15, lines 9 to 11, the pH is adjusted from a mildly acidic pH to a mildly basic pH, and as such meets the limitation of claim 2.

WO 99/30731 differs from claims 1-15 in not teaching a) the use of needle shaped crystals of GLP-1 analogs, b) GLP-1 solution having a purity of less than 95%, as measured by HPLC, c) wherein the GLP-1 analog is Arg^{34}GLP-1(7-37)or Arg^{26}GLP-1(7-37), and d) wherein the GLP-1 analog is attached to a lipophilic substituent. However, on Example 45, the reference of EP 0 619 322 clearly discloses the process of making needle shaped crystals of a GLP-1 analog and product thereof. Further, the

reference of Pidal et al., states on page 54, left column, last paragraph that the purity of GLP-1 was determined by capillary electrophoresis and analytical HPLC was <95%, thus, clearly meets the limitation of claim 5 which is directed to a GLP-1 analog in the aqueous solution having a purity of less than 95% as measured by HPLC. Furthermore, the reference of WO 98/08871 discloses method for producing GLP-1 analog wherein the GLP-1 analog is attached to lipophilic substituent and wherein the GLP-1 analog is Arg^{34}GLP-1(7-37)or Arg^{26}GLP-1(7-37), See e.g. page 17, lines 33 to pages 30, lines 6.

Therefore, in view of the above, one of ordinary skill in the art would have been motivated to adapt the conventional secondary references teachings of using needle shaped crystals of GLP-1 attached to lipohilic substituent having a purity of less than 95%, as measured by HPLC and wherein the GLP-1 analog is Arg^{34}GLP-1(7-37)or Arg^{26}GLP-1(7-37) into the method of the primary reference of WO 99/30731 because including such features into the method of WO 99/30731 reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages for producing crystals of GLP-1 analog which involves preparing an aqueous solution comprising a GLP-1 analog, a salt, and an organic solvent including a homogenous composition of GLP-1 crystals for pharmaceutical formulation thereof. With respect to claim 13, the claim is in product-by-process format, and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, *In re Brown*, 173 USPQ 685 (CCPA 1972); *In re Wertheim*, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, *In re Best*, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to Applicants. *In re Fitzgerald*, 205 USPQ 594. Therefore, the combined teachings of the prior art makes obvious a method for producing crystals of GLP-1 analogs, such as

needle shaped crystals and a pharmaceutical formulations thereof, absence of sufficient objective factual evidence or unexpected results to the contrary.

CONCLUSION AND FUTURE CORRESPONDANCE

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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Mohamed/AAM

August 25, 203